Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe

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Abstract

Preventing influenza infection early after transplantation is essential, given the disease's high mortality. A multicentre prospective cohort study in adult solid organ transplant recipients (SOTR) receiving the influenza vaccine during four consecutive influenza seasons (2009–2013) was performed to assess the immunogenicity and safety of influenza vaccination in SOTR before and 6 months after transplantation. A total of 798 SOTR, 130 of them vaccinated within 6 months of transplantation and 668 of them vaccinated more than 6 months since transplantation. Seroprotection was similar in both groups: 73.1% vs. 76.5% for A/(H1N1)pdm (p 0.49), 67.5% vs. 74.1% for A/H3N2 (p 0.17) and 84.2% vs. 85.2% for influenza B (p 0.80), respectively. Geometric mean titres after vaccination did not differ among groups: 117.32 (95% confidence interval (CI) 81.52, 168.83) vs. 87.43 (95% CI 72.87, 104.91) for A/(H1N1)pdm, 120.45 (95% CI 82.17, 176.57) vs. 97.86 (95% CI 81.34, 117.44) for A/H3N2 and 143.32 (95% CI 103.46, 198.53) vs. 145.54 (95% CI 122.35, 174.24) for influenza B, respectively. After adjusting for confounding factors, time since transplantation was not associated with response to vaccination. No cases of rejection or severe adverse events were detected in patients vaccinated within the first 6 months after transplantation. In conclusion, influenza vaccination within the first 6 months after transplantation is as safe and immunogenic as vaccination thereafter. Thus, administration of the influenza vaccine can be recommended as soon as 1 month after transplantation.

Keywords: Early vaccination, immune response, influenza vaccine, seroprotection, solid organ transplantation
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Introduction

After the 2009 influenza pandemic, substantial morbidity and mortality due to influenza infection was described in solid organ transplant recipients (SOTR) [1]. Given the risk of severe disease in this population, recommendations for diagnosis, prevention and therapy of influenza infection were given by several scientific societies [2–4].

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Time since transplantation has been associated with a higher risk of complications due to influenza infection in transplant recipients. Patients diagnosed with influenza infection within the first 3 months after receiving a transplant have a five times greater risk of developing severe disease compared to those infected after the first 3 months after transplantation [5]. Current recommendations, mostly based on expert opinion, support influenza vaccination after 3 months after transplantation [6,7]. More recent recommendations state that not vaccinating may leave a transplant recipient vulnerable to influenza infection for an entire influenza season. However, results of immunologic response to influenza vaccination during the first 6 months after transplantation are controversial [2,8]. While some authors reported a lower response [6,9], others found a similar response independent of the time since transplantation [10]. In addition, most of the studies with patients vaccinated within the first 6 months after transplantation are small series.

Although no solid evidence exists indicating that vaccination can cause acute rejection, there has been worry that nonspecific immune activation caused by vaccination could result in transplant rejection. In this context, safety should be the primary consideration when administering the influenza vaccine early after transplantation. Despite the need for preventing influenza infection in the first 6 months after transplantation, solid evidence regarding the efficacy and safety of influenza vaccination is lacking. Further, adequately sized studies are needed to clarify and firmly establish recommendations regarding the optimal timing of influenza vaccination in the transplant setting.

We hypothesized that early vaccination of SOTR had similar immunologic responses to SOTR vaccinated 6 months after transplantation. Thus, the aim of the study was to assess the immunogenicity, efficacy and safety of influenza vaccination in SOTR before and after 6 months since transplantation.

Material and Methods

Subjects and study design

We performed a multicentre prospective cohort study of influenza vaccinated SOTR during four consecutive influenza seasons. Kidney, heart and liver recipients older than 15 years of age who received one dose of the influenza vaccine between November 2009 and January 2013 were enrolled in 12 Spanish university hospitals belonging to the Spanish Network for Research in Infectious Diseases (REIPI). Patients were excluded if they received the transplant less than 1 month before immunization, if they had an allergy to any of the vaccine components or if they were pregnant. Serum samples were collected from each patient at the time of vaccination (baseline) and 5 weeks after vaccination. Patients were followed up during 90 days and up to 10 months if influenza infection or adverse effects were detected to evaluate the clinical efficacy of the vaccine. The study procedures were approved by the University Hospital Ethic Committee for Clinical Research according with the Helsinki Declaration of the World Medical Association. All patients provided written informed consent.

Clinical parameters and definitions

Baseline characteristics, immunologic and clinical response and adverse effects, including graft rejection and mortality, were recorded using a standardized questionnaire. Biopsies and histologic evaluation of graft rejection were only performed in cases of suspicion if signs of biochemical, echocardiographic or spirometry testing disorders were detected. Comorbidities were assessed by the Charlson comorbidity index [11].

Rejection was defined by the Banff and International Society for Heart and Lung Transplantation criteria [12]. Chronic renal insufficiency was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 for more than 3 months (modified criteria of the Kidney Disease Improving Global Outcomes) [13]. The definition of chronic liver disease was that of the Charlson comorbidity index [11]. Induction therapy was considered when administered within the 6 months before vaccination. Hypogammaglobulinemia was defined as IgG levels lower than 700 mg/dL. The general immunosuppressive regimens consisted of mycophenolate mofetil, calcineurin inhibitor and prednisone. Heart and kidney transplant recipients with medium-high immunologic risk for graft rejection or delayed introduction of tacrolimus received induction therapy with anti–interleukin 2 receptor monoclonal antibodies or polyclonal anti-thymocyte globulin. For liver transplant patients where induction therapy was indicated, anti–interleukin 2 receptor monoclonal antibody therapy was used.

Vaccines

Patients from the 2009–2010 influenza season received the pandemic H1N1-2009 (A/California/7/2009-H1N1) monovalent MF59-adjuvanted vaccine (Focetria, Novartis, Siena, Italy). Patients from the 2010–2011 and 2011–2012 influenza seasons received the trivalent nonadjuvant inactivated vaccine (Gripavac, Sanofi-Pasteur MSD, Madrid, Spain) containing the following strains: A/California/7/2009-H1N1, A/Perth/16/2009-H3N2 and B/Brisbane/60/2008. Patients from the 2012–2013 influenza season received one dose of the trivalent nonadjuvant inactivated vaccine (Mutagrip, Sanofi-Pasteur MSD) with the following strains: A/California/7/2009-H1N1, A/Victoria/361/2011-H3N2 and B/Wisconsin/1/2010. Adverse events were assessed according to established criteria [14].

Microneutralization assay

Microneutralization assays were performed as previously described [1,15] with some modifications (Supplementary Materials). The average absorbance (A450) from the quadruplicate wells of virus-infected (VC) and uninfected (CC) control wells was determined, and the neutralizing endpoint was determined by using a 50% specific signal calculation. The end point titre was expressed as the reciprocal of the highest dilution of serum with an A450 value less than *x*, where *x* = [(average A450 of VC wells) − (average A450 of CC wells)]/2. Sera were considered positive if titres were ≥40 obtained in at least two independent assays. Vaccination efficacy parameters were as follows: geometric mean titre (GMT), defined as mean antibody titre in the group of vaccinated individuals; seroprotection rate as percentage of subjects with antibody titre ≥1:40; seroconversion rate as percentage of subjects with a fourfold increase in antibody titres from baseline; and geometric mean ratio, defined as seroconversion factor after vaccination to before vaccination.

Statistical analysis

Patients were grouped by timing of influenza vaccination after transplantation into two groups, early and late. Patients in the early group received the influenza vaccine less than 6 months after transplantation, and patients in the late group received the influenza vaccine more than 6 months after transplantation. A descriptive statistical analysis was performed. Continuous variables were expressed as median and interquartile range or mean ± standard deviation if adjusted to normal distribution, and evaluated by Shapiro-Wilk or Kolmogorov-Smirnov tests when appropriate. The main primary outcome for the analysis was seroprotection. Secondary outcomes were seroconversion, GMT after vaccination, safety and clinical effectiveness. For bivariate analysis, the chi-square test, Fisher's exact test or the McNemar test were used for categorical variables, and Bonferroni correction was applied when appropriate. For quantitative variables, the Mann-Whitney test or Student's *t* test were used. If the variance was not homogeneous (Levene test), the Welch test was applied (ANOVA). For multivariate analysis, mixed-effects regression models were performed to control the effect of time since transplantation with possible confounding variables. Factors associated in the bivariate analysis and those considered clinically relevant were included in the models. For immunogenicity analysis, the geometric mean antibody titres at each time point were used. Relative risk and 95% confidence interval (CI) were calculated by taking the exponent of natural logarithm of the mean and 95% CI. Results were analyzed by PASW Statistic 18.0.1 software. Statistical significance was established as a p value of <0.05. All reported p values were based on two-tailed tests.

Results

Patient characteristics

A total of 798 SOTR (38.8% liver, 41.7% kidney, 19.4% heart) were included in the study. The early vaccination group was composed of 130 patients (16.2%) (median time to vaccination, 4.7 months, interquartile range 3.5–5.7 months) and 668 SOTR (83.8%) were in the late vaccination group (median time to vaccination, 44.5, months, interquartile range 18.4–96.1 months). Patients were more frequently men (69.8%), and the median age was 56 years (interquartile range 47.0–63.0 years). The type of transplant was liver in 333 cases (41.7%), kidney in 310 (38.8%) and heart in 155 (19.4%). Comorbidities appeared in 80.5% of cases, with diabetes mellitus and chronic heart disease being the most frequent (Table 1).

Baseline antibody titres

At baseline, 393 patients (49.2%) had preexisting antibody titres for A/(H1N1)pdm, 345 (70.3%) for influenza A/H3N2 and 392 (79.8%) for influenza B. Prevaccination antibody titres and GMT were significantly higher in the early vaccination group for influenza A/(H1N1)pdm and influenza B (Table 2).

Immunologic response to vaccination

Overall, there were no significant differences in the rate of seroprotection between patients in the early or late vaccination groups. The respective seroprotection rates for influenza A/(H1N1)pdm were 73.1% vs. 76.5% (p 0.49), 67.5% vs. 74.1% for influenza A/H3N2 (p 0.17) and 84.2% vs. 85.2% for influenza B (p 0.80). After vaccination, the proportion of seroprotected patients before and after vaccination changed significantly (p < 0.001) in both cohorts for the three viruses studied (Supplementary Table 1).

GMT after transplantation was similar (p > 0.05) for the early and late vaccination groups, respectively, as follows: 117.32 (81.52–168.83) vs. 87.43 (72.87–104.91) for influenza A/(H1N1)pdm, 120.45 (82.17–176.57) vs. 97.86 (81.34–117.44) for influenza A/H3N2 and 143.32 (103.46–198.53) vs. 145.54 (122.35–174.24) (Table 2).

Immunologic response to vaccination was also analyzed excluding patients with seroprotection at baseline. In these patients, the seroconversion rates in the early and late vaccination groups were, respectively, as follows: 61.1% and 71.6% (p 0.048) for A/(H1N1)pdm, 46.4% and 57.9% (p 0.18) for A/H3N2 and 85.7% and 78.0% (p 0.26) for influenza B.

No differences were observed when we analyzed the immune response according to transplanted organ (Supplementary Table 2).

In the early vaccination group of 130 SOTR, the seroprotection rate was similar among patients stratified according to the

TABLE 1. Characteristics, comorbidities and background of solid organ transplant recipients receiving influenza vaccinations between 2009 and 2013

Variable	Total (n = 798)	Early group (n = 130)	Late group (n = 668)	RR (95% CI)/β coefficient (95% CI)
Cohort				
2009–2010	284 (35.5)	14 (10.7)	270 (40.4)	0.26 (0.16, 0.44)
2010–2011	95 (11.9)	10 (7.6)	85 (12.7)	0.60 (0.32, 1.13)
2011–2012	88 (11.0)	24 (18.4)	64 (9.5)	1.92 (1.25, 2.96)
2012–2013	331 (41.4)	82 (63.0)	249 (37.2)	1.35 (1.48, 1.64)
Male sex	557 (69.8)	94 (72.3)	463 (69.3)	0.80 (0.65, 0.98)
Age (years), median (range)	56.0 (47.0–63.0)	54.0 (44.0–62.0)	56.0 (47.0–56.0)	−0.001 (−0.003, 0.001)
Type of transplant				
Kidney	310 (38.8)	45 (34.6)	265 (39.7)	1.4 (1.12, 1.73)
Liver	333 (41.7)	77 (59.2)	256 (38.3)	1.54 (1.30, 1.83)
Heart	155 (19.4)	8 (6.2)	147 (22.0)	0.19 (0.09, 0.38)
Immunosuppressive therapy				
Tacrolimus	559 (70.1)	113 (86.9)	446 (66.8)	2.08 (1.89, 2.29)
Mycophenolate mofetil	605 (75.8)	101 (77.6)	504 (75.6)	1.06 (0.95, 1.17)
Cyclosporine	159 (19.9)	10 (7.7)	149 (22.3)	0.34 (0.18, 0.63)
mTOR inhibitors	106 (13.3)	7 (5.4)	99 (14.8)	0.36 (0.17, 0.76)
Antibody induction	63 (7.8)	37 (29.1)	26 (3.9)	7.31 (4.59, 11.6)
Comorbidity				
Chronic liver disease	91 (11.4)	10 (7.7)	81 (12.1)	0.63 (0.33, 1.19)
Diabetes mellitus	196 (24.5)	22 (16.9)	176 (26.3)	0.64 (0.43, 0.95)
Chronic heart disease	162 (20.3)	27 (20.8)	135 (20.2)	1.02 (0.71, 1.48)
Chronic kidney disease	150 (18.8)	14 (10.8)	136 (20.4)	0.52 (0.31, 0.88)
Hypogammaglobulinemia	131 (16.4)	35 (29.2)	96 (16.5)	1.87 (1.33, 2.62)
Previous season influenza vaccination	539 (67.5)	83 (63.6)	456 (69.5)	0.93 (0.81, 1.07)
Cohort 2009–2010	166 (58.4)	5 (35.7)	161 (59.6)	1.07 (0.72, 1.61)
Cohort 2010–2011	70 (73.6)	6 (60.0)	64 (75.3)	0.79 (0.47, 1.34)
Cohort 2011–2012	79 (89.7)	19 (79.2)	60 (93.8)	0.84 (0.68, 1.04)
Cohort 2012–2013	223 (67.3)	52 (64.2)	171 (72.2)	0.88 (0.74, 1.06)

Data are presented as n (%) unless otherwise indicated. Parameters were compared by multiple comparison chi-square test or linear regression.
CI, confidence interval; RR, relative risk.

months elapsed since transplantation (Supplementary Table 3). Of them, 21 patients (16.1%) were vaccinated within the first 3 months after receiving the transplant, with postvaccination seroprotection rates of 80.0% for influenza A/(H1N1)pdm, 76.1% for influenza A/H3N2 and 76.1% for influenza B, and with seroconversion rates of 71.4% for influenza A/(H1N1)pdm, 47.6% for influenza A/H3N2 and 42.8% for influenza B. These parameters were not different from those vaccinated afterward.

Time since transplantation to vaccination (early vs. late), when controlled for other possible confounding factors, did not contribute to explain the variability of the seroprotection after vaccination or the GMT after vaccination for all virus types

TABLE 2. Antibody response against influenza A/(H1N1)pdm, A/H3N2 and B virus according to time from transplant to vaccination

Variable	Early group	Late group	p	RR (95% CI)/β coefficient (95% CI)
Baseline seroprotection rate, n (%)				
A/(H1N1)pdm	60 (46.2)	226 (33.8)	0.007	1.36 (1.10, 1.68)
A/H3N2	51 (44.7)	166 (44.5)	0.947	1.15 (0.89, 1.47)
B	78 (68.4)	182 (52.0)	0.002	1.53 (1.27, 1.83)
Postvaccine seroprotection rate, n (%)				
A/(H1N1)pdm	95 (73.1)	507 (76.5)	0.494	0.96 (0.86, 1.07)
A/H3N2	77 (67.5)	277 (74.1)	0.172	0.99 (0.84, 1.16)
B	96 (84.2)	299 (85.2)	0.800	1.14 (1.01, 1.29)
Seroconversion rate, n (%)				
A/(H1N1)pdm	68 (52.3)	379 (56.7)	0.352	0.92 (0.77, 1.10)
A/H3N2	53 (46.5)	175 (46.9)	0.936	1.13 (0.89.1.44)
B	45 (39.5)	179 (51.1)	0.030	0.89 (0.69, 1.16)
GMT (95% CI)				
A/(H1N1)pdm				
Baseline	32.59 (23.59, 45.03)	31.93 (26.33, 38.73)	0.000	0.02 (0.01, 0.04)
After vaccination	117.32 (81.52, 168.83)	87.43 (72.87, 104.91)	0.287	0.008 (−0.007, 0.02)
A/H3N2 (95% CI)				
Baseline	34.59 (24.01, 49.82)	27.33 (22.92, 32.59)	0.109	0.01 (−0.004, 0.03)
After vaccination	120.45 (82.17, 176.57)	97.86 (81.34, 117.44)	0.140	0.01 (−0.005, 0.030)
B (95% CI)				
Baseline	54.19 (40.62, 72.28)	34.94 (29.54, 39.80)	0.002	0.03 (0.01, 0.06)
After vaccination	143.32 (103.46, 198.53)	145.54 (122.35, 174.24)	0.741	0.004 (−0.01, 0.02)
GMR (95% CI)				
A/(H1N1)pdm	3.59 (2.47, 5.23)	2.73 (2.23, 3.35)	0.051	−0.01 (−0.02, 0.00)
A/H3N2	3.48 (2.50, 4.84)	3.58 (2.90, 4.14)	0.921	−0.001 (−0.02, 0.01)
B	2.64 (1.82, 3.83)	4.16 (3.39, 5.10)	0.039	−0.02 (−0.04, −0.001)

Parameters were compared by multiple comparison chi-square test or linear regression.
CI, confidence interval; GMT, geometric mean titre; GMR, geometric mean ratio; RR, relative risk.

studied in mixed-effects regression models (Tables 3–5). The presence of baseline antibody titres was associated with higher rates of seroprotection for all three types of influenza viruses: 79.8% vs. 71.6% for influenza A/(H1N1)pdm (p 0.01), 79.9% vs. 55.2% for influenza A/H3N2 (p < 0.001) and 89.3% vs. 67.7% for influenza B (p < 0.001), as well as higher posttransplant GMT: 134.03 vs. 83.71 for influenza A/(H1N1)pdm (p < 0.001), 126.03 vs. 53.65 for influenza A/H3N2 (p < 0.001) and 164.37 vs. 99.34 for influenza B (p 0.002; Tables 3–5).

Kidney transplant recipients had lower seroprotection rates compared to liver transplant recipients to influenza A/(H1N1) pdm (odds ratio (OR) 0.60, 95% CI 0.38, 0.94) and influenza A/H3N2 (OR 0.34 95% CI 0.19, 0.62). Patients with heart transplants had a lower seroprotection rate for influenza A/H3N2 (OR 0.37 95% CI 0.17, 0.79) and influenza B (OR 0.28 95% CI 0.11, 0.68) compared to liver transplant recipients (Tables 3–5).

Clinical failure to influenza vaccine

Nine patients (1.1%) were diagnosed with influenza disease a median of 35 days after vaccination (range 8–73 days), and 5 (55%) were admitted to hospital. Eight patients were in the late vaccination group (88.8%) and one in the early vaccination group (p 0.1). All patients had mild symptoms, and none developed graft rejection, died or required intensive care (Supplementary Table 4).

Vaccination safety

One kidney recipient vaccinated 118 months after transplantation (influenza season 2012–2013) was diagnosed with chronic graft rejection 83 days after receipt of the transplant. The decrease in creatinine clearance started before vaccination and was chronologically related to the onset of rifampicin therapy administered to treat miliary tuberculosis.

No other adverse events were detected in patients in the early or late vaccination groups.

Discussion

The present study shows that influenza vaccination of SOTR is safe and effective after the first month after transplantation, with a rate of seroprotection and GMT similar to that obtained in patients vaccinated after 6 months since transplantation.

The response to influenza vaccination in the transplant population ranges from 15% to 90% [1,10,15–24]. Factors such as lung transplant [18,25] and use of immunosuppressants (mycophenolate mofetil or mTOR (mammalian target of rapamycin) inhibitors) [1,6,16] have been related to decreased antibody response. However, it remains unresolved whether the strong immunosuppressive regimens provided in the first months after transplantation affect the response to influenza vaccine. While Lawal et al. [9] described that only 1 (14%) of 7 patients receiving the influenza vaccine within 4 months after liver transplantation responded to vaccination, Birdwell et al. [10] concluded that the protection achieved was similar between the 19 kidney transplant recipients who received the vaccine less that 6 months after transplantation compared to the 34 patients vaccinated more than 6 months after transplantation. A recent randomized study, comparing intradermal versus intramuscular influenza vaccination in a cohort of 212 SOTR, found an association in the univariate but not in the multivariate analysis between receiving the vaccine before 6 months since transplantation with a poor vaccine response [6].

TABLE 3. Mixed-effects regression model of factors influencing postvaccine seroprotection and GMT response to influenza A(H1N1)pdm grouped by time since transplantation[a]

	Postvaccine seroprotection[b]		Postvaccine GMT[c]	
Variable	**OR (95% CI)**	**p**	**β1 coefficient (95% CI)**	**p**
Age (years)	0.99 (0.98, 1.01)	0.43	0.001 (−0.009, 0.012)	0.81
Male (yes vs. no)	0.99 (0.67, 1.46)	0.94	0.19 (−0.09, 0.47)	0.19
Type of transplant				
Liver	Reference		Reference	
Kidney	0.60 (0.38, 0.94)	0.03	−0.43 (−0.74, −0.12)	0.006
Heart	0.76 (0.42, 1.38)	0.37	−0.37 (−0.76, 0.04)	0.07
Use of mTOR (yes vs. no)	1.37 (0.75, 2.51)	0.31	0.05 (−0.35, 0.44)	0.82
Diabetes (yes vs. no)	1.11 (0.71, 1.73)	0.66	−0.07 (−0.39, 0.24)	0.64
Hypogammaglobulinemia (yes vs. no)	0.72 (0.46, 1.12)	0.15	−0.32 (−0.65, 0.01)	0.06
Chronic kidney disease (yes vs. no)	0.98 (0.62, 1.55)	0.95	0.02 (−0.31, 0.34)	0.91
Chronic liver disease (yes vs. no)	0.80 (0.44, 1.46)	0.47	−0.09 (−0.52, 0.33)	0.67
Previous season vaccine (yes vs. no)	0.98 (0.65, 1.48)	0.94	−0.10 (−0.39, 0.19)	0.51
Baseline antibody titre (yes vs. no)	1.68 (1.15, 2.45)	0.01	0.55 (0.29, 0.81)	<0.001

CI, confidence interval; GMT, geometric mean titre; mTOR, mammalian target of rapamycin; OR, odds ratio.
[a]Group variable: time since transplant 2 to 6 months. Standard deviation: [b]1.59×10^{-10} and [c] 2.73×10^{-10}.

TABLE 4. Mixed-effects regression model of factors influencing postvaccine seroprotection and GMT response to influenza A/H3N2 grouped by time since transplantation[a]

	Postvaccine seroprotection[b]		Postvaccine GMT[c]	
Variable	**OR (95% CI)**	**p**	**β1 coefficient (95% CI)**	**p**
Age	0.98 (0.96, 1)	0.08	−0.01 (−0.03, 0.004)	0.17
Male (yes vs. no)	1.21 (0.73, 2.01)	0.46	0.14 (−0.22, 0.5)	0.45
Type of transplant				
Liver	Reference		Reference	
Kidney	0.34 (0.19, 0.62)	<0.001	−0.61 (−1.01, −0.21)	0.003
Heart	0.37 (0.17, 0.79)	0.01	−0.59 (−1.15, −0.04)	0.04
Use of mTOR (yes vs. no)	1.48 (0.66, 3.34)	0.34	0.09 (−0.46, 0.64)	0.74
Diabetes (yes vs. no)	0.98 (0.55, 1.73)	0.95	−0.13 (−0.53, 0.27)	0.53
Hypogammaglobulinemia (yes vs. no)	0.92 (0.54, 1.58)	0.780	−0.22 (−0.63, 0.19)	0.294
Chronic kidney disease (yes vs. no)	1.44 (0.74, 2.8)	0.29	0.37 (−0.1, 0.83)	0.12
Chronic liver disease (yes vs. no)	1.68 (0.74, 3.8)	0.21	0.53 (0.01, 1.05)	0.05
Previous season vaccine (yes vs. no)	1.24 (0.71, 2.15)	0.45	0.03 (−0.38, 0.44)	0.88
Baseline antibody titre (yes vs. no)	4.22 (2.56, 6.95)	<0.001	0.97 (0.6, 1.34)	<0.001

CI, confidence interval; GMT, geometric mean titre; mTOR, mammalian target of rapamycin; OR, odds ratio.
[a]Group variable: time since transplant 2 to 6 months. Standard deviation: [b]2.89×10^{-10} and [c]2.10×10^{-10}.

However, the number of patients vaccinated less than 6 months from transplantation was not specified.

It is crucial to define the correct time for influenza vaccination in transplant recipients. Thus, a delay in vaccination after transplantation may lead to vulnerability of transplant recipients to influenza infection, a period during which recipients are especially susceptible to influenza-related complications. As previously mentioned, little evidence is available regarding the immunogenicity of influenza vaccination within the first months after solid organ transplantation [2,4,5,9,10].

To our knowledge, the results presented here represent the largest cohort of SOTR receiving influenza vaccination within the first 6 months after receiving a transplant. We found that receiving the vaccine within 6 months after transplantation was not associated with a poor vaccine response when controlling for other possible confounding variables. The same findings were observed when only patients vaccinated during the first 3 months receiving a transplant were considered.

Nonseroprotected patients at baseline in the early post-transplantation group had a seroconversion rate that did not differ from those vaccinated thereafter. Previous results suggested that having baseline seroprotection promoted significantly higher GMT after vaccination compared to patients without baseline titres [15]. Patients vaccinated within the first 6 months after transplantation had significantly higher baseline titres for influenza A/(H1N1)pdm and influenza B, probably as a result of the remaining long-term influenza antibodies from the previous year's influenza vaccination. This finding, which to our knowledge has not been previously described, highlights the importance of vaccinating patients on transplant waiting lists or

TABLE 5. Mixed-effects regression model of factors influencing postvaccine seroprotection and GMT response to influenza B grouped by time since transplantation[a]

	Postvaccine seroprotection[b]		Postvaccine GMT[c]	
Variable	**OR (95% CI)**	**p**	**β1 coefficient (95% CI)**	**p**
Age	0.98 (0.96, 1.01)	0.2	−0.02 (−0.03, −0.01)	0.004
Male (yes vs. no)	0.95 (0.50, 1.79)	0.86	0.06 (−0.28, 0.40)	0.73
Type of transplant				
Liver	Reference		Reference	
Kidney	0.59 (0.28, 1.26)	0.18	−0.73 (−1.10, −0.35)	<0.001
Heart	0.28 (0.11, 0.68)	0.005	−1.02 (−1.56, −0.48)	<0.001
Use of mTOR (yes vs. no)	1.23 (0.47, 3.19)	0.67	0.11 (−0.41, 0.63)	0.67
Diabetes (yes vs. no)	1.22 (0.57, 2.61)	0.61	0.05 (−0.33, 0.44)	0.79
Hypogammaglobulinemia (yes vs. no)	1.12 (0.53, 2.39)	0.76	−0.04 (−0.44, 0.36)	0.84
Chronic kidney disease (yes vs. no)	1.48 (0.64, 3.41)	0.36	0.24 (−0.19, 0.67)	0.27
Chronic liver disease (yes vs. no)	1.22 (0.47, 3.13)	0.68	0.15 (−0.34, 0.64)	0.54
Previous season vaccine (yes vs. no)	0.60 (0.27, 1.30)	0.2	−0.06 (−0.43, 0.31)	0.75
Antibodies titre baseline (yes vs. no)	5.46 (2.82, 10.55)	<0.001	0.61 (0.22, 0.99)	0.002

CI, confidence interval; GMT, geometric mean titre; mTOR, mammalian target of rapamycin; OR, odds ratio.
[a]Group variable: time since transplant 2 to 6 months. Standard deviation: [b]0.198×10^{-10} and [c]6.24×10^{-11}.

with end-organ disease to improve their immunogenicity against influenza infection after transplantation.

The response to influenza vaccination had also been related to the type of virus included in the formulation, showing lower responses to influenza B [26] and responses that varied from 25.3% to 92.7% to different subtypes of influenza A virus [16,26,27]. In the present study, although there were some mild differences, overall, the response was similar within both cohorts for the three influenza strains across different influenza seasons.

A controversy concerning the risk of allograft rejection triggered by the immune response against the influenza vaccine has been raised in this population, with the rationale being that while the immunosuppression may diminish the immunogenicity of vaccination, influenza vaccination may stimulate a T cell response leading to organ rejection, which might be especially relevant in the early stages after receiving a transplant [28]. Previous studies involving SOTR receiving seasonal influenza vaccine did not found this relationship [16,19,28]. In our cohort, one patient (in the late vaccination group) experienced graft rejection after influenza vaccination. However, this patient had other possible causes of rejection, such as low immunosuppressive drug levels. In addition, episodes of acute allograft rejection and permanent graft dysfunction have also been related to seasonal and pandemic influenza virus infection [5,29,30].

Some limitations of the study need to be mentioned. First, some episodes of asymptomatic rejection might have not been diagnosed because routine biopsies were not performed. However, during patient follow-up, complications, including clinical evidence of rejection, were not detected. Second, asymptomatic influenza infection might have not been diagnosed. However, the extent to which these nonsymptomatic episodes may be related to the administration of the vaccine it is unknown. Third, although the number of patients who received the vaccine during the first 3 months might seem small, this is the largest reported series of patients vaccinated within the first 3 months of transplantation. Fourth, because only few patients received lymphocyte-depleting antibodies or rituximab therapy, our results may not be applicable to patients with this immunosuppression regimen. Finally, although the number of heart recipients vaccinated in the early vaccination group was small, influenza vaccine was safe for all patients, and the rate of seroprotection was above 67% for all influenza strains.

In summary, the results of the present study show that influenza vaccination is as safe and immunogenic in patients within the first 6 months after kidney and liver transplantation as in those vaccinated after 6 months since transplantation. Given the immunologic response, the lack of severe adverse events and the high rate of complications of influenza infection in the early posttransplantation period, administration of the influenza vaccine can be recommended as soon as 1 month after transplantation. In addition, compliance of pre-transplantation annual seasonal influenza vaccination in patients with end-organ disease should be pursued in order to promote better influenza immunologic protection early after transplantation.

Transparency Declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.07.014.

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